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10/054,490	01/22/2002	Walter Prikoszovich	100-7664F/C5	6537

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EXAMINER	
FISHER, ABIGAIL L	

ART UNIT	PAPER NUMBER
1616	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/054,490	PRIKOSZOVICH, WALTER	
	Examiner	Art Unit	
	ABIGAIL FISHER	1616	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *29 May 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *56,57,60,64,66-68 and 74-83* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *56,57,60,64,66-68 and 74-83* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Receipt of Amendments/Remarks filed on May 29 2009 is acknowledged. Claims 1-55, 58-59, 61-63, 65 and 69-73 were/stand cancelled. Claim 83 was amended. Claims 56-57, 60, 64, 66-68 and 74-83 are pending.

Rejections and/or objections not reiterated from previous office actions are hereby withdrawn. The following rejections and/or objections are either reiterated or newly applied. They constitute the complete set presently being applied to the instant application.

Abstract

The objection of the abstract is **withdrawn** in light of applicant's amendments filed on May 29 2009.

Specification

The objection of the specification is **withdrawn** in light of Applicant's amendments filed on May 29 2009.

Modified Rejection Based on amendments in the reply filed on May 29 2009

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 56-57, 60, 64, 66-68 and 74-83 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The term "purified state" in claim 74 is a relative term which renders the claim indefinite. The term "purified state" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. The instant specification indicates that the polylactide meets two requirements, a metal ionic concentration of at most 10 ppm and color strengths of the reference solutions B_2-B_9 of the brown color test of the European Pharmacopeia. However, these requirements do not indicate the actual degree of purity. It is unclear, other than less than 10 ppm of a metal cation, how much impurity would meet the instant limitation of a purified state.

Response to Arguments

Applicants argue that one of ordinary skill in the art would appreciate that a polymer in the purified state is one which is both off-white to white in color and contains one or more metals in cationic form in a concentration up to 10 ppm.

Applicants' arguments filed May 29 2009 have been fully considered but they are not persuasive.

Firstly, just because a product is off-white to white does not mean that it is purified. Secondly, it is unclear if the only requirements for the purified polymer are the color and the concentration of metals. Thereby, if the polymer meets these

requirements then it is purified regardless of what else is present (i.e. unreacted monomers). Typically, purification is associated with a particular percentage of purity but the instant specification provides no guidance as to this particular purity.

Modified Rejection Based on amendments in the reply filed on May 29 2009

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Applicant Claims
2. Determining the scope and contents of the prior art.
3. Ascertaining the differences between the prior art and the claims at issue, and resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 56-57, 60, 64, 66-68 and 74-83 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bodmer et al (US Patent No. 5,538,739, cited in the Office action mailed on 11/28/07) in view of Brich et al. (GB 2,145,422, cited in the Office action mailed on 11/28/07) and Reiners et al (US Patent No. 4,879,402, cited in the Office action mailed on 11/28/07) or Bendix et al. (US Patent No. 4810775, cited on

PTO Form 1449) and in further view of Eliot et al. (A Manual of Inorganic Chemistry, 1876) and as evidenced by Sigworth et al. (Journal of the American Water Works Association, 1972).

Applicant Claims

Applicant claims a pharmaceutical composition comprising a polylactide polymer in a purified state wherein the polylactide polymer in a purified state is an ester of a polyol containing at least three hydroxy groups and is off-white to white in color and wherein the polylactide in a purified state contains one or more metals in cationic form wherein the one or more metals have a concentration up to 10 ppm and a hydrophilic or lipophilic drug.

Determination of the Scope and Content of the Prior Art (MPEP §2141.01)

Bodmer et al. teach sustained release formulations of drugs, particularly somatostatin or octreotide, in a biodegradable and biocompatible polymer carrier (column 1, lines 13-19). The preferred polymers are linear polyesters. Linear polylactide-co-glycolides which have a molecular weight between 25,000 and 100,00 and a polydisperability between 1.2 and 2 are taught (column 8, lines 1-4). One preferred polymatrix is poly(lactide-co-glycolide)glucose (abstract and examples). It is taught that sustained release formulations can be in the form of an implant or microparticle (column 12, lines 20-25). The molar ratio of lactide:glycolide is from about 75:25 to 25:75 including 60:40 to 40:60 (column 9, lines 18-20). Star polymers having a

molecular weight from 10,000 to 200,000 and a polydispersity from 1.7 to 3.0 are taught (column 8, lines 35-40). It is taught that the polyester are known and described in GB 2145422 to Brich et al. (column 8, lines 7-8 and example 4).

Ascertainment of the Difference Between Scope the Prior Art and the Claims *(MPEP §2141.012)*

Bodmer et al. do not teach the synthesis of the polyol esters and subsequently the purification of the polyol esters. However, this deficiency is cured by Brich et al. and Reiners et al. or Bendix et al.

Brich et al. teach the preferred synthesis of the polyol esters taught in Bodmer et al. It is taught that the ester is formed in the presence of a catalyst which makes ring opening and polymerization feasible. The preferred catalyst is Sn-octoate (page 2, lines 37-41). It is taught that the formed polyol ester produced may be purified and isolated in a conventional manner (page 2, line 47).

Reiners et al. teach synthesis of (meth)acrylic acid derivatives containing urethane prepared by reaction of a (meth)acrylic acid ester with diisocyanates and subsequent reaction with polyols (abstract). Example 5 teaches polymer formation utilized tin octoate. After the solvent is removed (after filtration over active charcoal) a colorless highly viscous liquid is produced.

Bendix et al. is directed to a process for purifying resorbable polyesters. It is taught that if it seems necessary, the actual precipitation may be preceded by additional purification stages such as filtering with the addition of activated charcoal. The polyester can then be precipitated from the polymer solution in the presence of a

precipitation agent (column 4, lines 5-13). Exemplified polyesters include poly(lactide-co-glycolide).

Bodmer et al. do not teach the respective color of the resulting polymer. However, this deficiency is cured by Reiners et al. and Eliot et al.

Reiners et al. teach in Example 5 teaches polymer formation utilized tin octoate. After the solvent is removed (after filtration over active charcoal) a colorless highly viscous liquid is produced.

Eliot et al. teach that charcoal is known not only to destroy odors but it removes colors as well. For this color removing purpose it has long been employed in the purification of sugar and of many chemical and pharmaceutical preparations. It is taught that almost any coloring matter can be removed from a solution by filtering the liquid through a layer of charcoal (page 308, 388.). It is also taught that charcoal can also absorb many other substances besides coloring matters such as sulphates and metals like gold or silver (page 309, first paragraph).

Finding of Prima Facie Obviousness Rationale and Motivation (MPEP §2142-2143)

It would have been obvious to one of ordinary skill in the art at the time of the instant invention to combine the teachings of Bodmer et al., Brich et al., and Reiners et al. or Bendix et al. and utilize activated charcoal in the purification of an ester of a polyol. One of ordinary skill in the art would have been motivated to utilize activated charcoal as Brich et al. teach that the synthesis of the polymers of Bodmer et al. include utilizing tin octoate as a catalyst and then purifying and isolating in a conventional

manner. Both Reiners et al. and Bendix et al. teach that in the purification of polymers it is known to utilize activated charcoal.

Regarding the claimed color, Eliot et al. teach that activated charcoal has been known for a long time to be utilized to remove unwanted colors in pharmaceutical preparations. Since Reiners et al. teach that filtration over active charcoal produces a colorless liquid, it is the examiner's position that utilizing activated charcoal in the purification of the polymers taught by Brich et al. would possess the same color as instantly claimed.

Regarding the claimed amount of metal ion present, the instant specification teaches that precipitation of the polylactide from an organic solvent contains about 2 ppm of the metal cation (page 1). Since Reiners et al. teach this type of precipitation to purify the polyesters, there is a reasonable expectation that it would possess about 2 ppm of the metal cation. However, additionally if activated charcoal is additionally utilized in the purification process, one of ordinary skill in the would expect even less metal cation. As evidenced by Sigworth et al., tin is the most readily adsorbed metal of any studied on activated carbon (page 33, left column, last paragraph).

Claim 83 is rejected under 35 U.S.C. 103(a) as being unpatentable over Bendix et al. in view of Sigworth et al.

Applicant Claims

Applicants claim a method of removing tin from a polylactide polymer comprising the step of contacting a polylactide polymer with activated charcoal.

Determination of the Scope and Content of the Prior Art (MPEP §2141.01)

Bendix et al. is directed to a process for purifying resorbable polyesters. Exemplified polyesters are poly(lactide-co-glycolide). It is taught that if it seems necessary the actual precipitation may be preceded by additional purification stages such as filtering with the addition of activated charcoal. The polyester can then be precipitated from the polymer solution in the presence of a precipitation agent (column 4, lines 5-13). Example 8 is directed to the purification of a poly(DL-lactide) utilizing only the precipitation technique wherein 138 ppm of the Sn catalyst was used in the reaction and 34 ppm remained after precipitation.

Ascertainment of the Difference Between Scope the Prior Art and the Claims *(MPEP §2141.012)*

Bendix et al. do not exemplify utilizing activated charcoal in the purification. However, Bendix et al. do teach that the actual precipitation may be preceded by purification by filtering with the addition of activated charcoal. Bendix et al. do explicitly state that the activated charcoal will remove the tin. However, this deficiency is cured by Sigworth et al.

Sigworth et al. is directed to the adsorption of inorganic compound by activated carbon. It is taught that tin is the most readily adsorbed metal of any studied on activated carbon (page 33, left column, last paragraph).

Finding of Prima Facie Obviousness Rationale and Motivation (MPEP §2142-2143)

It would have been obvious to one of ordinary skill in the art at the time of the instant invention to utilize activated charcoal in the purification of polylactide polymers. One of ordinary skill in the art would have been motivated to utilize activated charcoal as Bendix et al. teach that precipitation purification may be preceded by filtration with addition of activated charcoal. Therefore, one of ordinary skill in the art would have been motivated to additionally utilize activated charcoal in order to further purify the polymer as taught be Bendix et al.

Regarding the claimed removal of tin, since it was known at the time of the instant invention that tin is one of the most readily adsorbed metals, the purification step taught by Bendix et al. which includes filtration using activated charcoal would necessarily remove the tin. Furthermore, one of ordinary skill in the art would have been motivated to add activated charcoal if a tin catalyst is utilized since it was known that tin is readily adsorbed on the activated carbon.

Absent any evidence to the contrary, and based upon the teachings of the prior art, there would have been a reasonable expectation of success in practicing the instantly claimed invention. Therefore, the invention as a whole would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

Response to Arguments

Applicants argue that (1) the instant application is directed to a very specific composition, namely a polylactide polymer in a purified state and a hydrophilic or lipophilic drug. Importantly, the polylactide polymer is an ester of a polyol containing at least three hydroxyl groups and is off-white to white in color and the metal concentration is up to 10 ppm. The cited references do not suggest such a composition at least with regard to the claimed metal concentration. Applicants argue that appears that the examiner is trying to argue the metal concentration of the prior art is inherent. However, inherency can not be a possibility, it has to be certain. Applicant argue that (2) instant claim 83 requires contract of the activated charcoal with the polylactide polymer to reduce tin concentration and the cited references are deficient as Bendix contains no disclosure related to such a purification stage and Sigworth is directed to tin absorption from water. Sigworth's statement suggests unpredictability and therefore no reasonable expectation of success.

Applicants' arguments filed May 29 2009 have been fully considered but they are not persuasive.

Regarding applicant's first argument, the primary reference Bodmer et al. teach sustained release formulations of drugs, particularly somatostatin or octreotide, in a biodegradable and biocompatible polymer carrier. Therefore, Bodmer et al. teach the specific composition claimed of a polylactide ester and a hydrophilic or lipophilic drug. Bodmer et al. do not specify how the polymer is prepared or purified. However, Bodmer et al. do suggest the teachings of Brich et al. for how the polymers are prepared.

Therefore, Bodmer et al. suggests the combination of the teachings of Brich et al. Brich et al. teach polyol ester is formed in the presence of a catalyst which makes ring opening and polymerization feasible. The preferred catalyst is Sn-octoate and that the formed polyol ester produced may be purified and isolated in a conventional manner. However, Brich does not specify what the purification and isolation manner is. Reiners et al. teach synthesis of polymers utilized tin octoate (the same catalyst taught in Brich et al.). After the solvent is removed (after filtration over active charcoal) a colorless highly viscous liquid is produced. Bendix et al. is directed to a process for purifying resorbable polyesters. It is taught that if it seems necessary, the actual precipitation may be preceded by additional purification stages such as filtering with the addition of activated charcoal. The polyester can then be precipitated from the polymer solution in the presence of a precipitation agent. Exemplified polyesters include poly(lactide-co-glycolide). Therefore Bendix et al. and Reiners et al. suggest that conventional manner of purification and isolation is precipitation and filtration over active charcoal. This provides the motivation for one of ordinary skill in the art to utilize activated charcoal to purify the polymer. Since Reiners et al. teach that filtration provides a colorless liquid. It would be reasonable to believe that the polymer formed in Brich et al. would also be colorless (i.e. white to off-white). Bendix et al. is directed to a process for purifying resorbable polyesters. Exemplified polyesters are poly(lactide-co-glycolide). It is taught that if it seems necessary the actual precipitation may be preceded by additional purification stages such as filtering with the addition of activated charcoal. The polyester can then be precipitated from the polymer solution in the presence of a

precipitation agent. Example 8 is directed to the purification of a poly(DL-lactide) utilizing only the precipitation technique wherein 138 ppm of the Sn catalyst was used in the reaction and 34 ppm remained after precipitation. Example 10 utilizes precipitation and the tin content in the end product runs from none detectable to 9 ppm. Since Sigworth et al. teaches that tin is the most readily adsorbed metal of any studied on activated carbon, it would be expected to reduce the tin content as well. Therefore, utilization of precipitation and passage over activated charcoal would be expected to bring the tin content in the purified polymer to a level from where it isn't detectable to a level below 10 ppm based on the teachings of the cited prior art (specifically Bendix et al. and Sigworth et al.). Therefore, the examiner has a reasonable expectation that the conventional purification process taught in the prior art would leave the polyol esters in the same purified state as instantly claimed.

Regarding applicants second argument, while Bendix et al. do not exemplify utilizing activated charcoal it is clearly suggested as a purification stage. Since the rejection is made under 103 and does not need to exemplify all embodiments, only suggest. “Disclosed examples and preferred embodiments do not constitute a teaching away from the broader disclosure or non-preferred embodiment.” *In re Susi,* 440 F.2d 442, 169 USPQ 423 (CCPA 1971). Clearly purification with activated charcoal is suggested. Since the teachings of Bendix et al. teach that the purification is utilized to remove the residual monomer content as well as tin content (example 10), this suggests to one of ordinary skill that purification would lead to a reduction in both of these contents. Regarding the teachings of Sigworth, it is specifically taught that activated

charcoal absorbs tin. Therefore, it use in purification would reduce the tin content present. The study of Sigworth was directed to the use of activated charcoal to remove a variety of different metal from water. From the examiner's reading of page 390, Sigworth says its unpredictable to be sure what mechanism is responsible for metal removal. It then goes on to state those water officials are encouraged to try activated carbon as a means of removing unwanted impurities (page 391). However, since Sigworth clearly teaches that activated carbon absorbs tin, it's use in purification of polymers which is suggested by the art that teaches making the polymer would be expected to reduce the tin content by absorbing from the solution/suspension it is presented in.

Since activated charcoal was known to remove tin and remove coloring material, there is a reasonable expectation that purification of the esters of polyol utilizing precipitation and activated charcoal would produce a polymer that is white to off-white and contains little if any tin. Therefore, the rejection is maintained since applicant has not provided any persuasive arguments to overcome the rejection.

Conclusion

No claims are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to ABIGAIL FISHER whose telephone number is (571)270-3502. The examiner can normally be reached on M-Th 9am-6pm EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Johann Richter can be reached on 571-272-0646. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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AF

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